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PAPER

The Pulmonary Effect of Nitric Oxide Synthase Inhibition Following Endotoxemia in a Swine Model

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Objective: To evaluate the pulmonary effect of treatment with *N*-nitro-L-arginine methyl ester (NAME) with and without inhaled nitric oxide (NO) in a swine model of endotoxemia.

Design: Randomized controlled trial.

Setting: Laboratory.

Interventions: Following a 20-minute intravenous infusion of *Escherichia coli* lipopolysaccharide (LPS) (200 μg/kg), animals were resuscitated with saline solution (1 mL/kg per minute) and observed for 3 hours while mechanically ventilated (fraction of inspired oxygen [F_{IO_2}], 0.6; tidal volume, 12 mL/kg; positive end-expiratory pressure, 5 cm H_2O). Group 1 (LPS, n=6) received no additional treatment; group 2 (NAME, n=5) received NAME (3 mg/kg per hour) for the last 2 hours; group 3 (NO, n=6) received NAME (3 mg/kg per hour) and inhaled NO (40 ppm) for the last 2 hours; and group 4 (control, n=5) received only saline solution without LPS.

Main Outcome Measures: Cardiopulmonary variables and blood gases were measured serially. The multiple inert gas elimination technique was performed at 3 hours. The wet-to-dry lung weight ratio was measured following necropsy.

Results: Administration of LPS resulted in pulmonary arterial hypertension, pulmonary edema, and hypoxemia with increased ventilation perfusion ratio mismatching. None of these changes were attenuated by NAME treatment alone but all were significantly improved by the simultaneous administration of inhaled NO.

Conclusions: Systemic NO synthase inhibition failed to restore hypoxic pulmonary vasoconstriction following LPS administration. The deleterious effects of endotoxemia on pulmonary function can be improved by inhaled NO but not by systemic inhibition of NO synthase.

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SEPSIS RESULTS in a systemic inflammatory response that is mediated by various cytokines and activated leukocytes. Systemic vasodilation and hypotension characteristic of sepsis have been hypothesized to occur secondarily to endogenous overproduction of nitric oxide (NO).[1,2] In contrast to the systemic vasodilatory response, pulmonary vasoconstriction and pulmonary arterial hypertension caused by the release of potent vasoconstrictors usually occurs.[3] Despite this pulmonary vasoconstrictive response, we and others[4-6] have found that hypoxic pulmonary vasoconstriction (HPV) is blunted and blood flow to poorly and unventilated lung areas is maintained. This loss of the hypoxic vasoconstrictive response adversely affects pulmonary oxygenation by increasing the ventilation perfusion ratio (VA/Q) mismatching. Because respiratory failure following sepsis is a significant comorbid factor, therapy aimed at attenuating this deleterious process may exert a beneficial effect on outcome.

Hypoxic pulmonary vasoconstriction is a mechanism that modulates pulmonary gas exchange by matching the distribution of blood flow to ventilation.[7,8] However, the cellular mechanisms that initiate and maintain HPV remain poorly understood. The mechanism responsible for the failure of HPV is even more unclear, although local overproduction of NO as well as vasodilatory prostaglandins such as prostacyclin have been hypothesized to play a role.[9,10] Inhibition of endogenous NO synthase (NOS) has been reported to

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MATERIALS AND METHODS

ANIMALS AND PREPARATIONS

Twenty-two Yorkshire swine of either sex (weighing a mean [±SD] of 20.7±1.5 kg) were used. The animals were housed in outdoor-covered runs and allowed commercial chow and water ad libitum. All study protocols were approved by the local animal research use committee and adhered to the provisions of the Animal Welfare Act.

On the day of the study, the animals were intubated with an orotracheal tube and instrumented while anesthetized with xylazine hydrochloride (2 mg/kg intramuscularly) and inhaled isoflurane (*United States Pharmacopeia*, 1% to 2% in 100% oxygen). Silastic cannulas were placed in a femoral artery and vein. One radiopaque sheath introducer, through which a Swan-Ganz catheter was placed, was inserted into an external jugular vein. Following cannulation, the animal was anesthetized and paralyzed for the duration of the study with intravenous fentanyl citrate (0.05-mg/kg bolus and 0.1 mg/kg per hour), xylazine hydrochloride (0.2 mg/kg per hour), and pancuronium bromide (0.2-mg/kg bolus followed by 0.2 mg/kg per hour). All of the animals were maintained in the dorsal position in a sling while being mechanically ventilated (fraction of inspired oxygen [F_{IO_2}], 0.6; tidal volume, 12 mL/kg; positive end-expiratory pressure, 5 cm H_2O) for the duration of the study. A 30-minute equilibration period was allowed prior to further manipulation.

PROTOCOL

The animals were randomly assigned to one of four groups. At baseline, animals in groups 1, 2, and 3 received an infusion of *Escherichia coli* lipopolysaccharide (LPS) (200 μg/kg, LPS 0111:B4) over 20 minutes. All animals were resuscitated with normal saline solution (1 mL/kg per minute) beginning at baseline. Animals in group 1 (LPS, n=6) received no additional treatment. Animals in group 2 (NAME, n=5) received a continuous infusion of *N*-nitro-L-arginine methyl ester (NAME) (Sigma Chemical Co, St Louis, Mo) (3 mg/kg per hour), a competitive inhibitor of NOS, starting 40 minutes after completion of the LPS infusion for the duration of the study. Animals in group 3 (NO, n=6) received a continuous infusion of NAME (3 mg/kg per hour) and 40 ppm of inhaled NO starting 40 minutes after completion of the LPS infusion and for the duration of the study. To administer a low concentration of NO, NO gas was first mixed with nitrogen using a standard blender. This gas mixture was delivered into the inspiratory limb of the ventilator and both NO and F_{IO_2} concentrations were measured distally and were individually adjusted to the desired concentration. Animals in group 4 (control, n=5) received only saline solution without LPS. All of the animals were observed for 3 hours from the initiation of the LPS or saline infusion. The multiple inert gas elimination technique (MIGET) was performed at 3 hours. Wet-to-dry lung weight ratios were measured following necropsy.

MEASUREMENTS

Cardiopulmonary variables and blood gases were measured at baseline and every 30 minutes during the study period. Pulmonary artery pressure, pulmonary capillary wedge pressure (PCWP), and systemic arterial pressure were measured using a pressure monitor. Blood gas analyses were performed using an IL 1303 pH/blood gas

enhance HPV.[11-13] The present study evaluated the role of NO on HPV in a swine model of endotoxemia.

RESULTS

All of the animals survived the observation period. The nitrogen dioxide concentration of the inspired gas was less than 1 ppm at all times.

Figure 1 depicts the serial mean pulmonary arterial pressure (MPAP) for the four groups. Treatment with LPS caused a significant increase in MPAP ($P<.05$) while treatment with NAME further increased MPAP. Simultaneous administration of NO and NAME in the NO group reduced MPAP significantly compared with the LPS or NAME groups. The serial pulmonary vascular resistance indexes are shown in **Figure 2**. They were significantly increased following LPS administration and further elevated by the use of NAME. Simultaneous administration of NO decreased the pulmonary vascular resistance index significantly compared with the NAME group during the last 2 hours of the study.

Administration of LPS resulted in a significant decline in oxygenation as indexed by the serial P_{aO_2}/F_{IO_2} ratios and arterial-alveolar oxygen pressure difference. NAME alone did not alleviate the hypoxemia, but simultaneous administration of NO improved oxygenation compared with LPS or NAME given during the last 2 hours (**Figure 3** and **Figure 4**).

Table 1 contains the serial PCWP and Qs/Qt measurements. Treatment with LPS or NAME did not affect the PCWP at any time point. The PCWP in the NO group was significantly less than in the NAME group at the 3-hour point. Administration of LPS increased Qs/Qt significantly and NAME alone did not improve Qs/Qt. There was decreased venous admixture in the NO group compared with the LPS or NAME groups. The P_{aCO_2} and methemoglobin levels did not change over time in any group and were not different between the groups (data not shown).

Table 2 contains the results of MIGET analysis. Treatment with LPS alone caused a significant increase in blood flow to true shunt (VA/Q=0) and high VA/Q (10<VA/Q<100) areas but not low VA/Q areas. Blood flow dispersion on the log axis of VA/Q (log SDQ) was also increased by LPS administration. Ventilation to high VA/Q areas (10<VA/Q<100) and the mean VA/Q value for ventilation were also increased by treatment with LPS. Treatment with NAME did not decrease blood flow to true shunt and thus did not restore HPV. Treatment with inhaled NO significantly decreased blood flow to true

analyzer and an IL 282 co-oximeter. Cardiac output was measured every hour by the thermodilution technique. Oxygen, NO, and nitrogen dioxide concentrations of the inspired gas were measured with gas monitors.

Peak inspiratory pressure, inspiratory tidal volume, and esophageal pressure were recorded by a pulmonary monitor every 30 minutes. Dynamic and static lung compliance, arterial-alveolar oxygen pressure difference, and physiologic pulmonary shunt fraction (Qs/Qt) were calculated using standard formulas.

After 3 hours, the pulmonary VA/Q distribution was measured using MIGET according to the method developed by Wagner et al.[14] A lactated Ringer's solution containing six inert gases (sulfur hexafluoride, ethane, cyclopropane, halothane, diethylether, and acetone) was infused at a rate of 0.1 mL/kg per minute. After 30 minutes, when equilibration of gas exchange had occurred, samples of arterial and mixed venous blood (10 mL each) were drawn anerobically into preweighed heparinized syringes. Mixed expired gas was collected through a temperature-controlled copper coil (outer diameter, 3.5 cm; length, 550 cm) 1 minute after blood sampling. Duplicate blood and expired gas samples were immediately analyzed on a gas chromatograph (Hewlett-Packard 5890-series 2, Hewlett-Packard Co, Palo Alto, Calif). To differentiate halothane from isoflurane, each sample was also analyzed on a gas chromatograph mass spectrometer (Hewlett-Packard 5988). Retention (the ratio of the concentration in arterial blood to that in mixed venous blood) and excretion (the ratio of the concentration in expired gas to that in mixed venous blood) of each of the six gases were calculated. The VA/Q distributions on a 50-compartment scale were computed from the retention and excretion partition coefficients using a computer program designed specifically for MIGET analysis.

Following euthanasia, the wet-to-dry lung weight ratio was determined by a modification of the gravimetric method of Drake et al.[15] The right lung was removed after the bronchi and vessels were ligated. The entire lung was homogenized with an identical weight of distilled water. Duplicate samples of the homogenate and arterial blood were weighed and dried at 80°C. Dry weights were measured and the wet-to-dry weight ratio calculated. A sample of the homogenate was centrifuged at 14 500 rpm for 1 hour, and a blood sample was diluted with the same volume of distilled water. To determine the hemoglobin levels in the homogenate and blood, 20 μL of the homogenate supernatant or the diluted blood was added to 2.5 mL of Drabkin's solution. The absorbance of both solutions was measured spectrophotometrically at 540 mm. The blood weight in the wet lung was calculated. From these data, blood-free wet and dry weights were determined and the wet-to-dry lung weight ratio was calculated.

HISTOLOGIC EVALUATION

Histologic evaluation of the pulmonary parenchymal injury of each animal was performed by light microscopy. The lung specimens were harvested from the same locations in the lobes of the left lung.

STATISTICAL ANALYSIS

Statistical analysis was performed using analysis of variance with Tukey's method to compare groups at equivalent time points. Data are shown as mean±SEM and significance was assigned at $P<.05$.

shunt and increased the percentage of normal VA/Q areas ($0.1<VA/Q<10$) compared with LPS or NAME, thus correcting the VA/Q mismatching.

Table 3 contains the serial peak inspiratory pressures and changes from baseline of dynamic and static lung compliance. Peak inspiratory pressures significantly increased and both static and dynamic lung compliance decreased over the 3 hours following endotoxin injection. NAME did not alleviate these changes at any time point. Inhaled NO attenuated the increase in peak inspiratory pressure and the decrease of both static and dynamic lung compliance compared with NAME, but the difference was not significant.

Pulmonary edema as indexed by the wet-to-dry lung weight ratio was significantly increased by LPS and was not affected by NAME infusion. Inhaled NO starting 1 hour after LPS infusion reduced the wet-to-dry lung weight ratio in the NO group compared with the NAME group (**Figure 5**).

Diffuse inflammation with sequestered polymorphonuclear leukocytes in both the alveoli and interstitium was evident in all animals following LPS administration. NAME or inhaled NO did not alter the histopathologic changes characteristic of LPS-induced lung injury.

COMMENT

Normally, the pulmonary circulation responds to acute hypoxia by vasoconstriction, a response that has been termed *hypoxic pulmonary vasoconstriction*.[7,8] Hypoxic pulmonary vasoconstriction may be elicited uniformly throughout the pulmonary circulation by exposing the entire lung to hypoxia or more locally by restricting ventilation to isolated lung segments.[16,17] Despite the obvious physiologic significance of this response and the fact that it was first described in 1946 by von Euler and Liljestrand,[18] the mechanism by which it occurs remains obscure.[7,8,18] Both the direct effects of hypoxia on the vasculature and the release of a vasoactive mediator from some site within the lung have been proposed as potential mediators of this phenomenon.

Failure of HPV has been reported to occur in various lung injury models, including those inducing injury by LPS, oleic acid, hyperoxia, and platelet-activating factor. The onset of this vasoregulatory dysfunction in such models is rapid and persists for a prolonged period.[19] Because the effector(s) of HPV in normal lungs remains unknown, the mechanism resulting in its failure in disease is even more obscure.

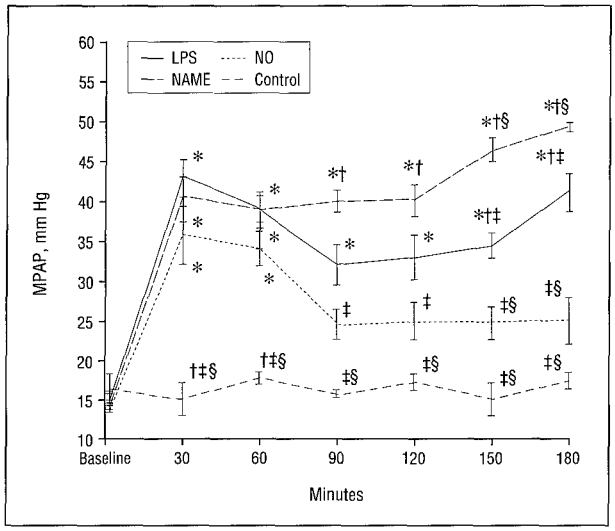

Figure 1. *The mean pulmonary arterial pressure (MPAP) was increased in the lipopolysaccharide (LPS)-treated group, further increased in the N-nitro-L-arginine methyl ester (NAME)–treated group, and restored to nearly normal in the inhaled nitric oxide (NO)–treated group compared with the control group. Asterisk indicates P<.05 compared with the control group; dagger, P<.05 compared with the NO group; double dagger, P<.05 compared with the NAME group; and section mark, P<.05 compared with the LPS group.*

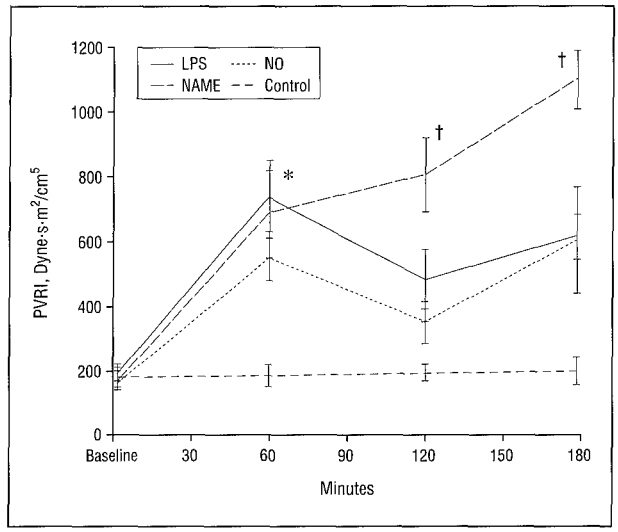

Figure 2. *The pulmonary vascular resistance index (PVRI) was increased in the lipopolysaccharide (LPS)-treated group and further exacerbated in the N-nitro-L-arginine methyl ester (NAME)–treated group. Asterisk indicates P<.05 for the control group vs the LPS, NAME, and nitric oxide (NO) groups; dagger, P<.05 for the NAME group vs the control, NO, and LPS groups.*

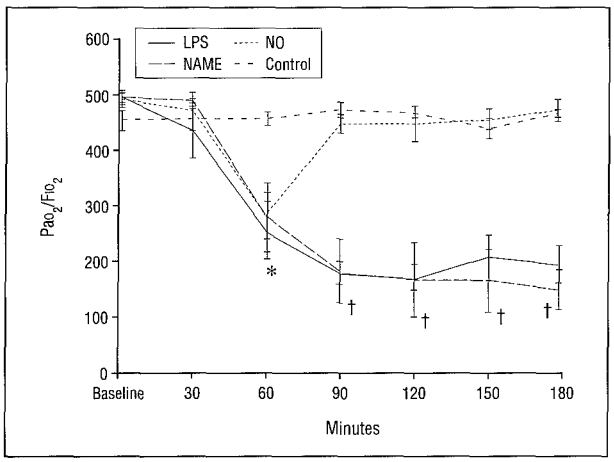

Figure 3. *The ratio of arterial oxygen pressure to fraction of inspired oxygen (Pao_2/Fio_2) was significantly reduced in the lipopolysaccharide (LPS)-treated group, not affected in the N-nitro-L-arginine methyl ester (NAME)–treated group, but was restored to normal in the inhaled nitric oxide (NO)–treated group. Asterisk indicates P<.05 for the control group vs the LPS, NAME, and NO groups; dagger, P<.05 for the control and NO groups vs LPS and NAME groups.*

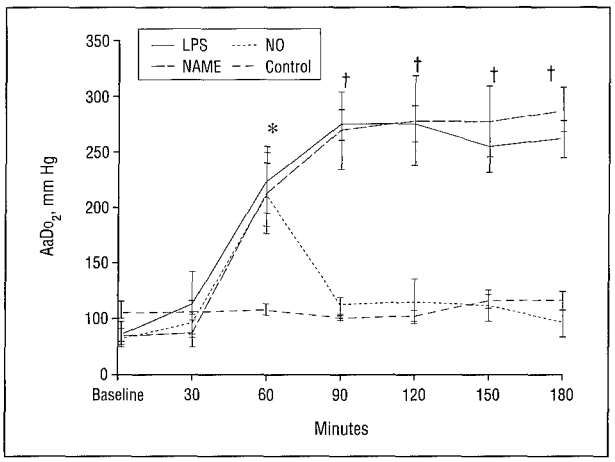

Figure 4. *The arterial-alveolar oxygen pressure difference ($AaDo_2$) was significantly increased in the lipopolysaccharide (LPS)-treated group, unaffected in the N-nitro-L-arginine methyl ester (NAME)–treated group, and corrected in the inhaled nitric oxide (NO)–treated group. Asterisk indicates P<.05 for the control group vs the LPS, NAME, and NO groups; dagger, P<.05 for the control and NO groups vs the LPS and NAME groups.*

The proposed role of NO as a regulator of basal vascular tone makes altered NO metabolism an attractive candidate as a mediator of failed HPV. Hypoxia-induced pulmonary vasoconstriction in vivo and in isolated lung models has been reported to be reversed by the administration of inhaled NO.[20-23] In addition, the inhibition of both NOS and guanylate cyclase in isolated pulmonary vessel preparations and intact lungs has been reported to enhance HPV.[9,11,24] Furthermore, it now appears that following endotoxemia, enhancement of NO production occurs on a systemic level and is partially responsible for the loss of systemic vascular tone. Thus, it is possible that when endothelial cells are damaged, there may be a loss of normal regulation of NO production and release resulting in abnormal and inappropriate vasodilation in areas of lung injury, thereby attenuating HPV despite the overall pulmonary vasoconstrictive response. If this hypothesis is true, then NOS inhibition should improve VA/Q mismatching following lung injury by restoring HPV.

In the present study, administration of *E coli* LPS induced significant pulmonary arterial hyertension, pulmonary edema, and VA/Q mismatching, resulting in arterial hypoxemia. The VA/Q mismatching as documented by MIGET was characterized by an increase in blood flow to true shunt (VA/Q=0) lung areas. The increase in blood flow to true shunt areas is in part a re-

Table 1. Serial Pulmonary Capillary Wedge Pressure (PCWP) and Physiologic Pulmonary Shunt (Qs/Qt) Measurements*

Measurement, by Study Group	Baseline	30 min	60 min	90 min	120 min	150 min	180 min
PCWP, mm Hg							
LPS	6.2±0.5	8.3±0.5	6.5±0.6	6.8±0.5	7.2±0.4	8.0±0.4	8.3±0.8
NAME	4.8±0.8	7.0±0.7	5.4±1.0	7.6±1.3	7.2±0.6	8.8±1.0	10.0±1.1†
NO	5.0±0.4	7.7±0.7	5.6±0.6	6.0±0.3	5.7±0.4	6.5±0.7	5.7±0.4‡
Control	6.8±0.8	6.5±1.5	8.0±0.5	8.0±1.0	7.6±0.7	6.5±0.5	7.8±0.8
Qs/Qt, %							
LPS	18±2	13±1	27±3§	37±1†§	44±6†§	43±8†§	43±7†§
NAME	19±2	14±2	25±2§	43±7†§	48±1†§	41±6†§	45±5†§
NO	16±2	12±1	25±2§	19±1‡‖	18±2‡‖	15±2‡‖	11±1‡‖
Control	15±1	18±2	17±1†‡‖	17±1‡‖	16±1‡‖	18±3‡‖	16±2‡‖

Data are given as mean±SEM.
†P<.05 *vs nitric oxide (NO) group.*
‡P<.05 *vs* N-*nitro-*L*-arginine methyl ester (NAME) group.*
§P<.05 *vs control group.*
‖P<.05 *vs lipopolysaccharide (LPS) group.*

Table 2. Results of Multiple Inert Gas Elimination Technique Analysis*

	Study Group			
	LPS	NAME	NO	Control
Q distribution				
VA/Q=0, %	36.7±10.1†‡	41.3±6.2†‡	1.9±0.9§‖	2.0±1.3§‖
10<VA/Q, %	3.9±1.0‡	4.6±0.7‡	3.3±1.4‡	0.4±0.2†§‖
Normal VA/Q, %	59.3±10.9†‡	54.0±6.7†‡	94.1±0.9§‖	96.4±2.4§‖
Mean VA/Q	0.91±0.20	1.10±0.10	1.17±0.24	1.19±0.20
Log SDQ	1.12±0.10‡	1.15±0.08†§	0.86±0.06‖	0.50±0.07§‖
V distribution				
Normal VA/Q, %	25.6±2.8‡	21.5±3.1‡	31.7±3.7‡	48.8±2.3†§‖
10<VA/Q<100, %	34.7±4.9‡	38.3±3.7‡	22.0±6.8	7.8±6.0§‖
100<VA/Q, %	39.7±5.3	40.2±2.0	46.3±3.0	43.4±3.9
Mean VA/Q	8.0±1.5‡	10.8±1.5‡	6.5±1.8	2.2±0.2§‖
Log SDV	1.54±0.25	1.50±0.05	1.50±0.08	0.93±0.21

Data are given as mean±SEM. Q indicates pulmonary blood flow; V, ventilation; VA/Q=0, true shunt; normal VA/Q, 0.1<VA/Q<10; 10<VA/Q, high VA/Q; 100<VA/Q, dead space; mean VA/Q, mean value of VA/Q distribution; log SDQ, Q dispersion on log VA/Q axis; and log SDV, V dispersion on log VA/Q axis.
†P<.05 *vs nitric oxide (NO) group.*
‡P<.05 *vs control group.*
§P<.05 *vs lipopolysaccharide (LPS) group.*
‖P<.05 *vs* N-*nitro-*L*-arginine methyl ester (NAME) group.*

sult of a decrease in ventilation to these lung segments secondary to vascular pressure–driven pulmonary edema and subsequent failure of HPV.

Meyer et al[25] reported that NOS inhibition significantly reduced pulmonary shunt fraction without improving gas exchange in an ovine model of endotoxemia. In a similar set of experiments, Leeman et al[9] reported that guanylate cyclase but not NOS inhibition using methylene blue and N-nitro-methyl-arginine, respectively, improved gas exchange following oleic acid infusion, thereby further clouding the role of NO in HPV failure. In the study herein, NOS inhibition using NAME failed to correct VA/Q mismatching in a porcine endotoxin lung injury model using a more sensitive measure of VA/Q, ie, MIGET. The lack of improvement of gas exchange in all three studies would indicate that NO does not mediate the failure of HPV in these models. It is possible that NOS inhibition failed to restore HPV because pulmonary arterial hypertension, which is a consistent finding following lung injury, has been reported to blunt HPV, and in all three studies, NOS inhibition further increased pulmonary arterial pressure. This augmentation of pulmonary hypertension implies that NO has a modulating function in regulating this vasoconstrictive response to lung injury. Because our model was acute, our data do not entirely rule out the possibility that NO plays a role in blunting HPV following LPS administration. Because of the short time course of our experiment, we can only conclude that inhibition of the constitutive form of NOS does not affect HPV. It is possible that in a more chronic model, the inducible form of NOS that requires synthesis of new enzyme following LPS administration may play a role in mediating HPV.

It has been suggested that vasodilatory prostaglandins are released following lung injury and inhibit HPV. Cyclo-oxygenase inhibition has been reported to improve VA/Q mismatching following endotoxin- and oleic acid–induced lung injury.[10,26,27] Inasmuch as

Table 3. Serial Peak Inspiratory Pressures (PIP) and Changes in Dynamic and Static Lung Compliance*

Measurement, by Study Group	Baseline	30 min	60 min	90 min	120 min	150 min	180 min
PIP, cm H_2O							
LPS	21.7±0.6	24.8±0.9	28.2±1.3†	29.8±0.8†	30.2±0.5†	32.3±0.5†	35.2±2.0†
NAME	20.2±0.7	23.8±1.0	26.6±1.3†	30.6±1.7†	31.4±1.3†	33.4±1.3†	35.4±1.0†
NO	21.2±1.1	24.5±1.3	26.3±1.7†	27.3±1.8†	29.3±2.1†	29.7±1.8	30.7±2.4†
Control	23.4±0.4	22.3±0.5	21.6±0.7‡	21.8±0.6‡	21.6±0.5‡	22.7±0.3‡	22.8±0.6‡
Change in dynamic lung compliance, %							
LPS	...	−26±7†	−47±5†	−51±6†	−51±4†	−55±4†	−61±4†
NAME	...	−24±5†	−39±5†	−49±10†	−53±7†	−57±7†	−61±5†
NO	...	−17±3†	−29±1†	−31±6†	−32±8†	−38±6†	−42±5†
Control	...	23±2‡	17±5‡	33±7‡	23±8‡	27±2‡	16±11‡
Change in static lung compliance, %							
LPS	...	−28±8†	−48±6†	−53±6†	−51±7†	−56±5†	−56±4†
NAME	...	−25±5†	−42±4†	−49±9†	−52±7†	−54±7†	−56±6†
NO	...	−19±4†	−31±3†	−35±5†	−39±6†	−42±7†	−42±7†
Control	...	18±10‡	17±6‡	29±14‡	24±11‡	14±7‡	10±12‡

Data are given as mean±SEM; changes in lung compliance are compared with baseline values.
†P<.05 *vs control group.*
‡P<.05 *vs lipopolysaccharide (LPS),* N-*nitro-*L*-arginine methyl ester (NAME), and nitric oxide (NO) groups.*

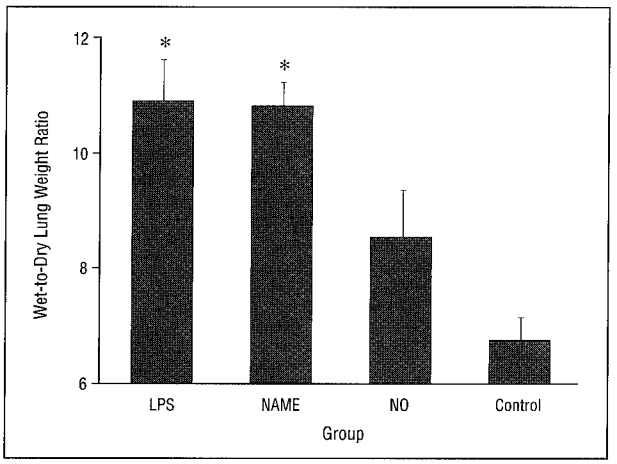

Figure 5. *Wet-to-dry lung weight ratios. The pulmonary water content was significantly increased in the lipopolysaccharide (LPS)-treated group; unaffected in the* N-*nitro-*L*-arginine methyl ester (NAME)–treated group; and significantly ameliorated in the inhaled nitric oxide (NO)–treated group. Asterisk indicates* P<.05 *compared with the control and NO groups.*

interstitial edema and other manifestations of the pulmonary insult are also ameliorated by such inhibition, it remains uncertain whether this represents the mechanism normally controlling restoration of HPV or a more global effect on the pulmonary injury.

Inhaled NO has been used as a rapid and potent selective pulmonary vasodilator. In animal studies, inhaled NO has been shown to attenuate pulmonary vasoconstriction following hypoxemia, exogenous administration of thromboxane analogues, heparin and protamine combination therapy, and sepsis.[28-30] This beneficial effect has been reported in patients with chronic pulmonary arterial hypertension, persistent pulmonary hypertension of the newborn, congenital heart failure, obstructive lung disease, pneumonia, and acute respiratory distress syndrome.[31-34]

We have reported that inhaled NO significantly improved VA/Q mismatching following sepsis by decreasing both true shunt and high VA/Q areas.[4] In the study herein, inhaled NO significantly attenuated pulmonary arterial hypertension, pulmonary edema, and hypoxemia despite NOS inhibition. Inhaled NO significantly improved VA/Q mismatching by dramatically decreasing blood flow to true shunt areas. These beneficial effects of inhaled NO were a result of decreased pulmonary edema and a specific vasodilatory effect in ventilated lung areas but not a restoration of HPV.

In summary, systemic inhibition of the constitutive isoform of NOS failed to restore HPV in true shunt areas following LPS administration. Inhibition of NOS further enhanced pulmonary arterial hypertension and did not alleviate pulmonary edema or hypoxemia. Simultaneous use of inhaled NO significantly improved VA/Q mismatching by decreasing blood flow to true shunt areas. Although NO appears to be a potent modulator of pulmonary vascular tone, overproduction of NO does not appear to be the cause of early VA/Q mismatching following LPS administration. Indeed, LPS-induced lung injury may reduce pulmonary NO production, resulting in a nonselective increase in pulmonary vascular resistance and no selective constriction in poorly ventilated segments. Inhaled NO appears to reestablish a dilation-constriction balance in the pulmonary circulation and thereby restores a physiologically more appropriate distribution of blood flow. Inhaled NO may be useful in the care of septic patients treated with systemic NOS inhibitors as a method to avoid further increases in pulmonary artery pressure and improve VA/Q mismatching.

The views of the authors do not purport to reflect the position of the Department of the Army or the Department of Defense.

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